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Besselink, Marc G. H.; van Santvoort, Hjalmar C.; van der Heijden, Geert J. M. G.; Buskens, Erik; Gooszen, H. G.; Dutch Acute Pancreatitis Study Grp

Published in:
Langenbecks Archives of Surgery

DOI:
[10.1007/s00423-008-0419-y](https://doi.org/10.1007/s00423-008-0419-y)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2009

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Besselink, M. G. H., van Santvoort, H. C., van der Heijden, G. J. M. G., Buskens, E., Gooszen, H. G., & Dutch Acute Pancreatitis Study Grp (2009). New randomized trial of probiotics in pancreatitis needed? Caution advised. *Langenbecks Archives of Surgery*, 394(1), 191-192. <https://doi.org/10.1007/s00423-008-0419-y>

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New randomized trial of probiotics in pancreatitis needed? Caution advised

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Received: 30 July 2008 / Accepted: 11 August 2008 / Published online: 8 October 2008
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Dear Sir,

We support the use of large-scale, high-quality, placebo-controlled randomized trials as much as Dr. Sun and co-workers do [1]. However, we do not support their rather strong conclusion that a new randomized trial of probiotic prophylaxis in patients with predicted severe acute pancreatitis is currently warranted.

In their meta-analysis, Sun et al. detected no significant effects of probiotic prophylaxis in patients with acute pancreatitis [1]. In our double-blind study on the effect of combined probiotic strains, which had a sample size almost five times larger than the previous studies, we detected a significant increase in both mortality and bowel ischemia [2]. These were all well-reputed probiotic strains that had been used for a long time without any negative effects being reported. The major difference between our study and the previous three studies is the much larger number of patients with concurrent organ failure. In their studies, Olah et al. included only four and 14 patients with multiorgan

failure, respectively [3, 4]. In contrast, our study included 64 patients with organ failure, including 48 patients with multiorgan failure with no significant differences at baseline between the groups [2]. The unexpected effect of probiotics in our study, i.e., nine cases of bowel ischemia including eight with fatal outcome, was solely present in patients with organ failure receiving probiotics. The sample size of the previous studies was obviously too small to detect the apparent potential negative effects of probiotics in patients with acute pancreatitis and concurrent organ failure.

In their discussion, Sun et al. suggest that the randomization in our study was “skewed” for organ failure. Their conclusion is based on their own post hoc calculation deducting patients that developed organ failure “on the day of randomization” from the total number of patients with organ failure. However, as explained in our manuscript [2], many patients that developed organ failure “on the day of randomization” had, by that time, already received one or two doses of probiotics. Therefore, the onset of organ failure “on the day of randomization” cannot be used as a parameter to conclude that randomization was “skewed.” Furthermore, there were no significant differences between the groups in any of the baseline characteristics. After correcting for the minor imbalances in organ failure and pancreatic necrosis present at baseline, mortality remained higher in the probiotics group. Finally, when excluding all patients with organ failure “on the day of randomization” from the analysis, mortality was still twice as high in the probiotics group and a significantly higher proportion of patients developed bowel ischemia in the probiotics group.

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Notably, in Fig. 3 of their paper, Sun et al. misquote the first study of Olah et al. [3] by stating that there was a *decrease* in incidence of systemic inflammatory response syndrome (SIRS) due to probiotic treatment: 41% SIRS (9/22) in the probiotics group vs 48% (11/23) in the control-group. Table 3 in the original paper reveals different data: 50% SIRS (11/22) in the probiotics group vs 26% (6/23) in the control group; the risk of SIRS was actually *increased* in patients receiving probiotics.

Our group has recently started experimental studies focusing on the impact of probiotic treatment in the hypoperfused gut. In a field where currently so many factors remain unclear, we would suggest the highest level of caution in launching any new randomized trial of probiotic prophylaxis in patients with predicted severe acute pancreatitis. We realize that one large trial, in general, is usually not sufficient to fully discard a certain treatment for an important indication as severe acute pancreatitis. However, we strongly disagree with their conclusion which is based on a meta-analysis in which three of the four

studies have serious methodological shortcomings and one well-designed study shows a significantly higher mortality after probiotic treatment without an acceptable explanation at this stage.

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